PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark
Office, PCT
2011 South Clark Place Room
CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 December 2000 (05.12.00)	
International application No. PCT/CA00/00440	**Applicant's or agent's file reference** 338-104PCT2
International filing date (day/month/year) 28 April 2000 (28.04.00)	**Priority date** (day/month/year) 28 April 1999 (28.04.99)
Applicant STEEVES, John, D. et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 November 2000 (15.11.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Charlotte ENGER
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

10/019365

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To:

MBM & Co.
Box 809, Station B
Ottawa, Ontario K1P 5P9
CANADA

Date of mailing *(day/month/year)*	23.02.2001
Applicant's or agent's file reference ~~338-104PCT2~~ 338-112 PCT	**REPLY DUE** **within 2 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00440 ✓	28/04/2000	28/04/1999

International Patent Classification (IPC) or both national classification and IPC

A61K39/395

Applicant

UNIVERSITY OF BRITISH COLUMBIA et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☒	Certain document cited
VII	☐	Certain defects in the international application
VIII	☒	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 28/08/2001.

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 0 Tx 523656 epmu d

Authorized officer / Examiner

Mennessier, T

Formalities officer (incl. extension of time limits)

Pedersen, C

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-64 as originally filed

Claims, No.:

1-27 as originally filed

Drawings, sheets:

1/13-13/13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ *contained in the international application in written form.*
- ☐ *filed together with the international application in computer readable form.*
- ☐ *furnished subsequently to this Authority in written form.*
- ☐ *furnished subsequently to this Authority in computer readable form.*
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

☐ the entire international application,

☒ claims Nos. 16-26,

because:

☒ the said international application, or the said claims Nos. 16-26 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 26 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☒ the claims, or said claims Nos. 25 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrialapplicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1, 3, 7-10 and 15-17 (no)
Inventive step (IS)	Claims	2, 4-6, 11-14, 18-24 and 27 (no)

Industrial applicability (IA) Claims

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Comments with respect to item III

a) Use of a composition in a medical treatment (claims 16-26)

Claims 16-26 are each directed to a use of a composition according to the invention in a medical treatment, i.e., relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

b) Lack of clarity (claim 26)

Claim 26 is directed to the "*use of one or more complement fixing antibodies [...] to enable the detection and monitoring of the use [of] the compositions of claim 1*",i.e., to enable the detection and monitoring of compositions comprising one or more of the said antibodies. Due to this confusing wording claim 26 as a whole is not clear. The precise subject-matter for which protection is sought cannot be precisely determined, the defect being such that no meaningful opinion could be formed.

c) Inadequat support (claim 25)

Claim 25 is directed to the use of a composition of claim 1 with the view to generating an environment within the mammalian CNS that is permissive to growth of transplanted cells. This particular aspect of the invention appears not to have been illustrated in the description. Furthermore, the sentence of page 40 (see lines 9-13) which only merely repeats the wording of claim 25 is inefficient at establishing that the claimed compositions are actually capable of generating an environment within the mammalian CNS that is permissive to growth of transplanted cells. In this respect, it has to be noted that at line 10 of page 40 it is only referred to the generation of an environment that is "relatively" permissive, which indicates how doubtful the generation of a favourable environment might be. Therefore, it has to be considered that claim 25 is inadequately supported by the description, the defect being such that no meaningful opinion could be formed.

2. Comments with respect to item V

a) Documents cited

Reference is made to the following documents:

D1: *The Journal of Neuroscience*, 15(10), 1995, 6963-74
D2: *Experimental Neurology*, 151, 1998, 303-13
D3: *Experimental Neurology*, 154, 1998, 12-22
D4: WO 99/21581

It appears that at least one of the authors of documents D1, D2 and D3 has been designated as an inventor in the present application. The Applicants and inventors for document D4 are the same as those for the present application.

b) Novelty (Article 33(2) PCT)

(i) Document D1 discloses a composition comprising an IgG1 polyclonal galactocerebroside (GalC) antibody (denoted AB142) at a dilution of 1:5 with 33% guinea pig complement (GIBCO BRL, # 19195-015) in 0.1 M PBS, pH 7.4 (see bottom of left-hand column of page 6964). Said composition was delivered by direct spinal cord injection or by osmotic pump to healthy or having undergoing spinal cord transection hatchling chicks (see also page 6964, both columns) and was proved to cause immunological myelin disruption. The authors concluded that their findings demonstrate that immunological myelin disruption within the hatchling chick spinal cord shortly after a thoracic transection facilitated partial neuroanatomical regeneration of axotomized brainstem-spinal projections in vivo (see left-hand column of page 6971).

(ii) Document D2 discloses a composition comprising also the AB142 antibody used at a dilution of 1:2 with 33% guinea pig complement in 0.1 M PBS, pH 7.4 (see bottom of left-hand column of page 304). The

said composition was injected into the exposed dorsal funiculus of adult rats, on which laminectomy of the first lumbar vertebra has been previously performed, and proved to cause immunological myelin disruption. In 10 animals, further laminectomy of the second lumbar vertebra was performed immediately after immunological demyelination. Later on axotomy within the exposed dorsal funiculus was carried out (see also page 304, both columns). The authors concluded that theirs results demonstrate that demyelination in the adult rat spinal cord facilitates axonal regeneration (see the paragraph bridging pages 307 and 308).

(iii) Document D3 reports on experiments which exactly correspond to those of Example I of the present application (compare pages 44-52 of the application with pages 13-18 of D3). As Example 1 of the application, D3 illustrates that the transient developmental suppression myelination or the disruption of mature myelin by local intraspinal infusion of a composition (see left-hand column of page 13) comprising both serum complement proteins (GIBCO BRL, 19195-015; i.e., guinea pig complement [see document D1]) and a complement-fixing, myelin-specific antibody (an antibody to galactocerebroside, AB142 being preferred) facilitated brainstem-spinal axonal regeneration after spinal transection in the adult rat.

(iv) In view of the above comments, it appears that the subject-matter of the following claims is not new:

over either of documents D1, D2 and D3:

- **claim 1** (directed to a composition comprising serum complement proteins along with a complement-fixing, myelin-specific antibody),

- **claim 3** (directed to said composition wherein the antibody is polyclonal),

- **claim 7** (directed to said composition wherein the antibody is an antibody to galactocerebroside),

- **claim 8** (directed to said composition in which the complement proteins include the C3 component),

- **claim 9** (directed to said composition wherein the complement proteins are derived from species different from that species to which it is administered),

- **claim 10** (directed to said composition wherein the complement proteins are a physically distinct component from the antibody component),

- **claim 11** (directed to said composition further comprising a physiologically acceptable carrier), and

- **claim 16** (directed to the use of said composition to transiently disrupt and/or transiently demyelinate, to promote neuron repair and/or regeneration in a subject),

over either of documents D2 and D3:

- **claim 17** (directed to said use wherein the subject is mammalian),

(v) In contrast, the subject-matter of **claims 2, 4-6, 11-14, 18-24 and 27** may be considered to be new, as being not disclosed in the relevant state of art, including documents D1, D2 and D3.

c) Inventive step (Article 33(3) PCT)

(i) **Claims 2, 4-6 and 11-14** are dependent on claim 1. They are directed to preferred compositions which in no way have been illustrated in the experimental part of the description. Whereas, as a result the IPEA is

deprived of any relevant information useful to assess whether the additional technical feature(s) they contain is/are associated with a technical effect which could not have been expected by the person skilled in the art aware of the state of the art including documents D1, D2 and D3, there can be no doubt that labelling the antibody of the composition (**claim 4**) or using antibody fragments rather than entire antibodies (**claims 5-6**) would provide advantages which are well-known to the said person. The same reasoning may also apply to the subject-matter of **claims 2 and 12-14** in view the statement on page 20 of document D3 according to which "*It is known that the beneficial of blocking CNS myelin-associated inhibitors on axonal regenration can be augmented by the concomitant application of growth factors, such as NT-3*". Therefore, the subject-matter of **claims 2, 4-6 and 11-14** is considered not to involve an inventive step.

(ii) **Claim 27** is directed to a kit comprising the composition of claim 1. Even if a kit is not disclosed *stricto sensu* in any of documents D1, D2 and D3, in view of the detailed description of the composition given in both documents D1 and D2, it has to considered that a person skilled in the art aware of the said documents would have regarded it as obvious to present such a composition in the form of a kit to be used in a medical treatment as defined in claim 16. Therefore, it has to be concluded that the subject-matter of **claim 27** does not involve an inventive step.

(iii) **Claim 18** is directed to the use according to claim 17 wherein the subject is human. **Claims 19-24** are dependent on claim 17. The subject-matter of said claims is in no way illustrated in the experimental part of the description. It is believed that the results obtained with the rat model as precisely reported in documents D2 and D3 would have enabled the person skilled in the art to extrapolate them without the exercise of inventive skill to the treatment of humans. Therefore, it is considered that the subject-matter of **claims 18-24** does not involve an inventive step. It has to be noted that if, in the absence of any detailed illustration of the medical treatment of humans in the description, the

exercise of inventive skill would be required the person skilled in the art should have considered that the description was insufficient to enable him to carry out said treatment.

(iv) In view of the above comments, it appears that the subject-matter of **claims 1-24 and 27** does not involve an inventive step.

d) Industrial applicability (Article 33(4) PCT)

(i) The subject-matter of **claims 1-15 and 27** may be considered to be susceptible of industrial applicability.

(ii) For the assessment of the present **claims 16-24** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

e) P-document (document D4)

(i) The present application appears to be closely related to document D4. The description of D4 has been used in the application with exactly the same wording. Only the following description passages and figures of the application are not present in D4: (i) form line 28 of page 14 to line 16 of page 15 [comments with respect to added Figures 11-13], (ii) line 26 of page 19, lines 24-32 of page 27, (iii) lines 10-21 of page 28 [comments corresponding to the added Example V], (iv) from line 23 of page 28 to line 18 of page 29, (v) from line 27 of page 29 to line 14 of page 39, (vi) from line 18 of page 41 to line 21 of page 42, (vii) Example V (see pages 63-64), and (vii) Figures 11-13 (which illustrate the results of Example V).

(ii) Also direct correspondences can be identified between the claims of the present application and those of D4 (compare (i) claims 1 and 2 of the application with claims 3 and 4 of D4, (ii) claims 3-25 of the application with claims 7-29 of D4, and (iii) claim 27 of the application with claim 35 of D4).

(iii) Should the priority appear not to have been validly claimed document D4, due to the overlapping pointed to above between it and the application, would have to be taken into consideration when examining whether the various aspects of the claimed subject-matter are new and involve an inventive step.

3. Comments with respect to item VI

Moreover, it appears that in view of their respective priority, filing and publication dates, the content of document D4 as filed whatever the validity of the priority might be taken into consideration by certain patent offices such as the EPO at the national/regional stage of the examination of the present application when assessing whether the various aspects of the claimed subject-matter are new.

4. Comments with respect to item VIII

In view of the comments made at points 1.b) and 1.c) above, claims 25 and 26 are objected to under Article 6 PCT.

10/019365

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For Receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 338-104PCTa

Box No. I TITLE OF INVENTION

COMPOSITION FOR NEURONAL REGENERATION

Box No. II APPLICANT

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

UNIVERSITY OF BRITISH COLUMBIA
2194 Health Sciences Mall
Room 331 - I.R.C. Building
Vancouver, BC V6T 1W5
Canada

☐ This person is also inventor.

Telephone No.

Facsimile No.

Teleprinter No.

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

STEEVES, John D.
CORD, Depts, Zoology, Anatomy & Surgery
6270 University Boulevard
Vancouver, British Columbia V6T 1Z4
Canada

This person is:

☐ applicant only

☒ applicant and inventor

☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MBM & Co.
P.O. Box 809
Station B
Ottawa, Ontario K1P 5P9
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Telephone No.
(613) 567-0762

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(613) 563-7671

Teleprinter No.

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

DYER, Jason K.
CORD, Depts, Zoology, Anatomy & Surgery
6270 University Boulevard
Vancouver, British Columbia V6T 1Z4
Canada

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: UK

State *(that is, country)* of residence: CA

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KEIRSTEAD, Hans S.
Reeve-Irvine Research Center
University of California at Irvine
2111 Gillespie Neuroscience Research Facility
Irvine, California 92697
U.S.A.

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOURQUE, Jason
3355 Cardinal Drive
Burnaby, British Columbia V5A 2T7
Canada

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality: CA

State *(that is, country)* of residence: CA

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

State *(that is, country)* of nationality:

State *(that is, country)* of residence:

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☐ the United States of America only
- ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No.V DESIGNATION OF STATES

The following designations are hereby made under Rule 4.9(a) *(mark the applicable check-boxes; at least one must be marked)*:

Regional Patent

☒ **AP** **ARIPO Patent:** **GH** Ghana, **GM** Gambia, **KE** Kenya, **LS** Lesotho, **MW** Malawi, **SD** Sudan, **SL** Sierra Leone, **SZ** Swaziland, **TZ** United Republic of Tanzania, **UG** Uganda, **ZW** Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT

☒ **EA** **Eurasian Patent:** **AM** Armenia, **AZ** Azerbaijan, **BY** Belarus, **KG** Kyrgyzstan, **KZ** Kazakhstan, **MD** Republic of Moldova, **RU** Russian Federation, **TJ** Tajikistan, **TM** Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** **European Patent:** **AT** Austria, **BE** Belgium, **CH and LI** Switzerland and Liechtenstein, **CY** Cyprus, **DE** Germany, **DK** Denmark, **ES** Spain, **FI** Finland, **FR** France, **GB** United Kingdom, **GR** Greece, **IE** Ireland, **IT** Italy, **LU** Luxembourg, **MC** Monaco, **NL** Netherlands, **PT** Portugal, **SE** Sweden, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** **OAPI Patent:** **BF** Burkina Faso, **BJ** Benin, **CF** Central African Republic, **CG** Congo, **CI** Côte d'Ivoire, **CM** Cameroon, **GA** Gabon, **GN** Guinea, **GW** Guinea-Bissau, **ML** Mali, **MR** Mauritania, **NE** Niger, **SN** Senegal, **TD** Chad, **TG** Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ **AE** United Arab Emirates
☒ **AL** Albania .....
☒ **AM** Armenia .....
☒ **AT** Austria .....
☒ **AU** Australia .....
☒ **AZ** Azerbaijan
☒ **BA** Bosnia and Herzegovina .....
☒ **BB** Barbados
☒ **BG** Bulgaria .....
☒ **BR** Brazil .....
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☒ **GE** Georgia .....
☒ **GH** Ghana .....
☒ **GM** Gambia
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☒ **HU** Hungary .....
☒ **ID** Indonesia
☒ **IL** Israel .....
☒ **IN** India .....
☒ **IS** Iceland
☒ **JP** Japan .....
☒ **KE** Kenya .....
☒ **KG** Kyrgyzstan .....
☒ **KP** Democratic People's Republic of Korea .....
☒ **KR** Republic of Korea .....
☒ **KZ** Kazakhstan .....
☒ **LC** Saint Lucia
☒ **LK** Sri Lanka
☒ **LR** Liberia
☒ **LS** Lesotho .....
☒ **LT** Lithuania
☒ **LU** Luxembourg
☒ **LV** Latvia
☒ **MA** Morocco .....
☒ **MD** Republic of Moldova .....
☒ **MG** Madagascar .....
☒ **MK** The former Yugoslav Republic of Macedonia .....
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☒ **UG** Uganda .....
☒ **US** United States of America .....
☒ **UZ** Uzbekistan .....
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☒ **YU** Yugoslavia .....
☒ **ZA** South Africa .....
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Check-boxes reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ all member states .....
☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. *(Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)*

Box No. VI PRIORITY CLAIM ☐ Further priority claims are indicated in the Supplemental Box.

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is: national application: country	regional application:* regional Office	international application: receiving Office
item (1) 28 April 1999	2,270,364	CA		
item (2)				
item (3)				

☒ The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of the present international application is the receiving Office)* identified above as item(s): (1)

** Where the earlier application is an ARIPO application, it is mandatory to indicate in the Supplemental Box at least one country party to the Paris Convention for the Protection of Industrial Property for which that earlier application was filed (Rule 4.10(b)(ii)). See Supplemental Box.*

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)* : ISA/

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority):*
Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII CHECK LIST; LANGUAGE OF FILING

This international application contains the following **number of sheets**:

request	: 4
description (excluding sequence listing part)	: 60
claims	: 3
abstract	: 1
drawings	: 14
sequence listing part of description	:
Total number of sheets	: 82

This international application is **accompanied** by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☒ copy of general power of attorney; reference number, if any: GPA 96/0097
4. ☐ statement explaining lack of signature
5. ☐ priority document(s) identified in Box No. VI as item(s):
6. ☐ translation of international application into (language):
7. ☐ separate indications concerning deposited microorganism or other biological material
8. ☐ nucleotide and/or amino acid sequence listing in computer readable form
9. ☐ other *(specify)*:

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. IX SIGNATURE OF APPLICANT OR AGENT

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).

MBM+Co.
MBM & Co. (Margaret Swain, Partner)

For receiving Office use only

1. Date of actual receipt of the purported international application:
2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:
4. Date of timely receipt of the required corrections under PCT Article 11(2):
5. International Searching Authority (if two or more are competent): ISA/
6. ☐ Transmittal of search copy delayed until search fee is paid.

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

The demand must be filed directly with the competent International Preliminary Examining Authority or, if two or more Authorities are competent, with the one chosen by the applicant. The full name or two-letter code of that Authority may be indicated by the applicant on the line below:

IPEA/ _____

10/019365

PCT

CHAPTER II

DEMAND

under Article 31 of the Patent Cooperation Treaty:
The undersigned requests that the international application specified below be the subject of international preliminary examination according to the Patent Cooperation Treaty and hereby elects all eligible States (except where otherwise indicated).

For International Preliminary Examining Authority use only	
Identification of IPEA	Date of receipt of DEMAND

Box No. I IDENTIFICATION OF THE INTERNATIONAL APPLICATION		Applicant's or agent's file reference 338-104PCT2
International application No. PCT/CA00/00440	International filing date *(day/month/year)* 28 April 2000 (28.04.2000)	(Earliest) Priority date *(day/month/year)* 28 April 1999 (28.04.99)

Title of invention
COMPOSITION FOR NEURONAL REGENERATION COMPRISING MYELIN-SPECIFIC ANTIBODIES AND COMPLEMENT PROTEINS

Box No. II APPLICANT(S)

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*	Telephone No.:
UNIVERSITY OF BRITISH COLUMBIA 2194 Health Sciences Mall Room 331 - I.R.C. Building Vancouver, British Columbia V6T 1W5 Canada	Facsimile No.: Teleprinter No.:

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

STEEVES, John D.
CORD, Depts. Zoology, Anatomy & Surgery
6270 University Boulevard
Vancouver, British Columbia V6T 1Z4
Canada

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

DYER, Jason K.
CORD, Depts. Zoology, Anatomy & Surgery
6270 University Boulevard
Vancouver, British Columbia V6T 1Z4
Canada

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
UK	CA

[X] Further applicants are indicated on a continuation sheet.

Sheet No. 2

national application No.
PCT/CA00/00440

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

KEIRSTEAD, Hans S.
Reeve-Irvine Research Centre
University of California at Irvine
2111 Gillespie Neuroscience Research Facility
Irvine, California 92697
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	US

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

BOURQUE, Jason
3355 Cardinal Drive
Burnaby, British Columbia V5A 2T7
Canada

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CA	CA

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

State *(that is, country)* of nationality:	State *(that is, country)* of residence:

☐ Further applicants are indicated on another continuation sheet.

[redacted]ational application No.
PCT/CA00/00440

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] has been appointed earlier and represents the applicant(s) also for international preliminary examination.

[ ] is hereby appointed and any earlier appointment of (an) agent(s)/common representative is hereby revoked.

[ ] is hereby appointed, specifically for the procedure before the International Preliminary Examining Authority, in addition to the agent(s)/common representative appointed earlier.

Name and address: *(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)*

MBM & Co.
P.O. Box 809
Station B
Ottawa, Ontario K1P 5P9
Canada

Telephone No.: (613) 567-0762

Facsimile No.: (613) 563-7671

Teleprinter No.:

[ ] **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special addr ess to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

1. The applicant wishes the international preliminary examination to start on the basis of:

[ ] the international application as originally filed

the description [ ] as originally filed
[ ] as amended under Article 34

the claims [ ] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [ ] as originally filed
[ ] as amended under Article 34

2. [ ] The applicant wishes any amendment to the claims under Article 19 to be considered as reversed.

3. [ ] The applicant wishes the start of the international preliminary examination to be postponed until the expiration of 20 months from the priority date unless the International Preliminary Examining Authority receives a copy of any amendments made under Article 19 or a notice from the applicant that he does not wish to make such amendments (Rule 69.1(d)). *(This check-box may be marked only where the time limit under Article 19 has not yet expired.)*

* Where no check-box is marked, international preliminary examination will start on the basis of the international application as originally filed or, where a copy of amendments to the claims under Article 19 and/or amendments of the international application under Article 34 are received by the International Preliminary Examining Authority before it has begun to draw up a written opinion or the international preliminary examination report, as so amended.

Language for the purposes of international preliminary examination: ENGLISH

[X] which is the language in which the international application was filed.
[ ] which is the language of a translation furnished for the purposes of international search.
[ ] which is the language of publication of the international application.
[ ] which is the language of the translation (to be) furnished for the purposes of international preliminary examination.

Box No. V ELECTION OF STATES

The applicant hereby elects all eligible States *(that is, all States which have been designated and which are bound by Chapter II of the PCT)*

excluding the following States which the applicant wishes not to elect:

None

Sheet No. 4

national application No.
PCT/CA00/00440

Box No. VI CHECK LIST

The demand is accompanied by the following elements, in the language referred to in Box No. IV, for the purposes of international preliminary examination:			For International Preliminary Examining Authority use only: received	not received
1. translation of international application	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	: 1	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

The demand is also accompanied by the item(s) marked below:

1. ☐ fee calculation sheet
2. ☐ separate signed power of attorney
3. ☐ copy of general power of attorney; reference number, if any:
4. ☐ statement explaining lack of signature
5. ☐ nucleotide and or amino acid sequence listing in computer readable form
6. ☐ other *(specify)*:

Box No. VII SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE

Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the demand).

MBM & Co. (Margaret Swain, Partner)

For International Preliminary Examining Authority use only

1. Date of actual receipt of DEMAND:
2. Adjusted date of receipt of demand due to CORRECTIONS under Rule 60.1(b):
3. ☐ The date of receipt of the demand is AFTER the expiration of 19 months from the priority date and item 4 or 5, below, does not apply. ☐ The applicant has been informed accordingly.
4. ☐ The date of receipt of the demand is WITHIN the period of 19 months from the priority date as extended by virtue of Rule 80.5.
5. ☐ Although the date of receipt of the demand is after the expiration of 19 months from the priority date, the delay in arrival is EXCUSED pursuant to Rule 82.

For International Bureau use only

Demand received from IPEA on:

From the INTERNATIONAL SEARCHING AUTHORITY

PCT 10/019365

To:
MBM & Co.
Box 809, Station B
Ottawa, Ontario K1P 5P9
CANADA

MBM & CO.
MARUSYK MILLER & SWAIN
SEP 13 2000
RECEIVED

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference: 338-104PCT2	Date of mailing (day/month/year): 07/09/2000
	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No.: PCT/CA 00/00440	International filing date (day/month/year): 28/04/2000
Applicant: UNIVERSITY OF BRITISH COLUMBIA et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46).

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

RECEIVED
DOCKETING
CALL UP: 10/7/00
DUE DATE: 11/7/00
BY: KD

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Catherine Humbert

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
338-104PCTa		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/CA 00/ 00440	28/04/2000	28/04/1999
Applicant		
UNIVERSITY OF BRITISH COLUMBIA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 5 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   COMPOSITION FOR NEURONAL REGENERATION COMPRISING MYELIN-SPECIFIC ANTIBODIES AND COMPLEMENT PROTEINS

5. With regard to the **abstract**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

International Application No
PCT/CA 00/00440

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/395 A61K38/17 G01N33/68 G01N33/577 A61P25/00
//C07K16/28,(A61K39/395,38:17)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
WPI Data, BIOSIS, EPO-Internal, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DYER J K ET AL: "Regeneration of brainstem-spinal axons after lesion and immunological disruption of myelin in adult rat." EXPERIMENTAL NEUROLOGY, (1998 NOV) 154 (1) 12-22. , XP002091206 the whole document --- -/--	1-27

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 August 2000	07/09/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040 Tx. 31 651 epo nl	

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KEIRSTEAD H S ET AL: "Axonal regeneration and physiological activity following transection and immunological disruption of myelin within the hatchling chick spinal cord." JOURNAL OF NEUROSCIENCE, (1995 OCT) 15 (10) 6963-74. , XP002091204 cited in the application abstract page 6971 -page 6973	1-27
X	DATABASE BIOSIS 'Online! BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 1997 KEIRSTEAD H S ET AL: "In vivo immunological suppression of spinal cord myelin development." Database accession no. PREV199800051022 XP002144605 abstract & BRAIN RESEARCH BULLETIN, vol. 44, no. 6, 1997, pages 727-734, ISSN: 0361-9230	1,16,27
X	KEIRSTEAD H S ET AL: "Identification of post-mitotic oligodendrocytes incapable of remyelination within the demyelinated adult spinal cord." JOURNAL OF NEUROPATHOLOGY AND EXPERIMENTAL NEUROLOGY, (1997 NOV) 56 (11) 1191-201. , XP002091207 abstract page 1193, last paragraph -page 1195, column 2, paragraph 3	1,7,16, 27
X	KEIRSTEAD H S ET AL: "A quantifiable model of axonal regeneration in the demyelinated adult rat spinal cord." EXPERIMENTAL NEUROLOGY, (1998 JUN) 151 (2) 303-13. , XP002091208 abstract	1,7,16, 27
P,X	WO 99 21581 A (DYER JASON K ;STEEVES JOHN D (CA); KEIRSTEAD HANS S (GB)) 6 May 1999 (1999-05-06) page 8, line 13 -page 9, line 6; claims 1-35	1-27

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 16-25 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
Although claim 26 (partially, as far as an in vivo method is concerned) is directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 00/00440

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Information on patent family members

International Application No
PCT/CA 00/00440

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9921581 A	06-05-1999	AU 9617998 A	17-05-1999

10/019365

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

MBM & Co.
Box 809, Station B
Ottawa, Ontario K1P 5P9
CANADA

RECEIVED
DOCKETING
CALL UP:
DUE DATE:
BY:

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

	Date of mailing *(day/month/year)* 19.07.2001
Applicant's or agent's file reference ~~338-104PCT2~~ 338-112pct	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00440	28/04/2000	28/04/1999

Applicant
UNIVERSITY OF BRITISH COLUMBIA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Digiusto, M

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
338-104PCT2		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA00/00440	28/04/2000	28/04/1999
International Patent Classification (IPC) or national classification and IPC A61K39/395		
Applicant UNIVERSITY OF BRITISH COLUMBIA et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 10 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 9 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/11/2000	19.07.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d	Authorized officer Mennessier, T

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-64	as originally filed			

Claims, No.:

1-59	as received on	04/07/2001	with letter of	23/06/2001

Drawings, sheets:

1/13-13/13	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☒ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)
see separate sheet

6. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 44-56.

because:

☒ the said international application, or the said claims Nos. 44-55 (with respect to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 56 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 1-55, 57, 58 and 59

	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-55, 57, 58 and 59
Industrial applicability (IA)	Yes:	Claims	1-43, 57, 58 and 59
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

1. Comments with respect to item I

The description as originally filed (see more particularly, page 33, lines 17-21) appears not to contain any supported evidence that the compositions of the invention may comprise, either in addition to cell adhesion molecules, fibronection, laminin, collagen, elastin, glycosaminoglycans, proteoglycans or growth factors or instead of the same, **bioactive fragments thereof**. Therefore, **claim 35** is considered to contain added matter which goes beyond the disclosure in the international application as filed, contrary to the requirements of Article 34(2)(b) PCT, last sentence. The same remark also applies to any claim which is dependent thereon or the subject-matter of which is defined with a back-reference to it (see **claims 38, 39, 44-55 and 57-59**).

2. Comments with respect to item III

a) Use of a composition in a medical treatment (claims 44-55)

Claims 44-55 are each directed to a use of a composition according to the invention in a medical treatment, i.e., relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

b) Lack of clarity (claim 56)

Claim 56 which has been derived from claim 26 as originally filed is directed to the "*use of one or more complement fixing antibodies [...] to detect and monitor the efficacy of the* ***composition*** *cause focal transient disruption and/or transient demyelination of mammalian neurons*" (emphasis added). As the composition referred to therein is not at all defined (in former claim 26 compositions of claim 1 were referred to) and due to a confusing wording [some term(s) is/are deemed to have been omitted between the terms "composition" and "cause"], the subject-matter of claim 56 as a whole is not clear. The precise subject-matter for which protection is sought cannot be precisely determined, the defect being such that no meaningful opinion could

be formed.

3. Comments with respect to item V

a) Preliminary remark

The following comments are restrictively made in that they do not concern the subject-matter of claim 56 (see point 2.b) above) and those parts of the subject-matter of **claims 35, 38, 39, 44-55 and 57-59** (see point 1 above) which do not meet the requirements of Article 34(2)(b) PCT.

b) Documents cited

(i) Reference is made to the following documents:

D1: *The Journal of Neuroscience*, 15(10), 1995, 6963-74
D2: *Experimental Neurology*, 151, 1998, 303-13
D3: *Experimental Neurology*, 154, 1998, 12-22
D4: WO 99/21581

(ii) It appears that at least one of the authors of documents D1, D2 and D3 has been designated as an inventor in the present application. The Applicants and inventors for document D4 are the same as those for the present application.

(iii) Document D1 discloses a composition comprising an IgG1 polyclonal galactocerebroside (GalC) antibody (denoted AB142) at a dilution of 1:5 with 33% guinea pig complement (GIBCO BRL, # 19195-015) in 0.1 M PBS, pH 7.4 (see bottom of left-hand column of page 6964). Said composition was delivered by direct spinal cord injection or by osmotic pump to healthy or having undergoing spinal cord transection hatchling chicks (see also page 6964, both columns) and was proved to cause immunological myelin disruption. The authors concluded that their findings demonstrate that immunological myelin disruption within the hatchling chick spinal cord shortly after a thoracic transection facilitated

partial neuroanatomical regeneration of axotomized brainstem-spinal projections in vivo (see left-hand column of page 6971).

(iv) Document D2 discloses a composition comprising also the AB142 antibody used at a dilution of 1:2 with 33% guinea pig complement in 0.1 M PBS, pH 7.4 (see bottom of left-hand column of page 304). The said composition was injected into the exposed dorsal funiculus of adult rats, on which laminectomy of the first lumbar vertebra has been previously performed, and proved to cause immunological myelin disruption. In 10 animals, further laminectomy of the second lumbar vertebra was performed immediately after immunological demyelination. Later on axotomy within the exposed dorsal funiculus was carried out (see also page 304, both columns). The authors concluded that theirs results demonstrate that demyelination in the adult rat spinal cord facilitates axonal regeneration (see the paragraph bridging pages 307 and 308).

(v) Document D3 reports on experiments which exactly correspond to those of Example I of the present application (compare pages 44-52 of the application with pages 13-18 of D3). As Example 1 of the application, D3 illustrates that the transient developmental suppression myelination or the disruption of mature myelin by local intraspinal infusion of a composition (see left-hand column of page 13) comprising both serum complement proteins (GIBCO BRL, 19195-015; i.e., guinea pig complement [see document D1]) and a complement-fixing, myelin-specific antibody (an antibody to galactocerebroside, AB142 being preferred) facilitated brainstem-spinal axonal regeneration after spinal transection in the adult rat.

c) Novelty (Article 33(2) PCT)

The claimed subject-matter as a whole may be considered to be new, as compositions comprising one or more complement-fixing antibodies and complement lacking one or more of the normal complement proteins appear not to be disclosed in the relevant state of the art, including documents D1,

D2 and D3.

d) Inventive step (Article 33(3) PCT)

(i) Whereas it is explained in the description (see page 26, lines 11-15) that removal from the whole complement of the C3 protein or the C4 protein results in a composition with reduced efficacy, the advantage(s) over the use of a whole complement (as referred to in each of the prior art documents D1, D2 and D3) which could be associated with the use of a depleted complement, which still contains C3 or C4 but which is deficient in one or more of the other normal other complement proteins, are not pointed out elsewhere in the description, including its experimental part.

(ii) As a result the subject-matter of independent **claims 1, 2, 5, 40, 42 and 44** is considered not to involve an inventive step over the teaching which may be derived from each of said documents. Furthermore, it is also considered that none of dependent **claims 3,4, 6-39, 41, 43, 45-55, 57, 58 and 59** contain any additional technical features which, in combination with the features of any claim to which they refer, would confer to the compositions referred to therein any unexpected avantage over the compositions of the state of the art (see Documents D1, D2 and D3). Therefore, it is considered that also the dependent claims do not meet the requirements of the PCT with respect to inventive step.

e) Industrial applicability (Article 33(4) PCT)

(i) The subject-matter of **claims 1-43 and 57-59** may be considered to be susceptible of industrial applicability.

(ii) For the assessment of the present **claims 44-55** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the

use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

f) P-document (document D4)

(i) The present application appears to be closely related to document D4. The description of D4 has been used in the application with exactly the same wording. Only the following description passages and figures of the application are not present in D4: (i) form line 28 of page 14 to line 16 of page 15 [comments with respect to added Figures 11-13], (ii) line 26 of page 19, lines 24-32 of page 27, (iii) lines 10-21 of page 28 [comments corresponding to the added Example V], (iv) from line 23 of page 28 to line 18 of page 29, (v) from line 27 of page 29 to line 14 of page 39, (vi) from line 18 of page 41 to line 21 of page 42, (vii) Example V (see pages 63-64), and (vii) Figures 11-13 (which illustrate the results of Example V).

(ii) Also direct correspondences can be identified between the claims of the present application and those of D4 (compare (i) claims 1 and 2 of the application as originally filed with claims 3 and 4 of D4, (ii) claims 3-25 of the application as originally filed with claims 7-29 of D4, and (iii) claim 27 of the application as originally filed with claim 35 of D4).

(iii) Should the priority appear not to have been validly claimed document D4, due to the overlapping pointed to above between it and the application, would have to be taken into consideration when examining whether the various aspects of the claimed subject-matter are new and involve an inventive step.

4. Comments with respect to item VI

Moreover, it appears that in view of their respective priority, filing and publication dates, the content of document D4 as filed whatever the validity of the priority

might be taken into consideration by certain patent offices such as the EPO at the national/regional stage of the examination of the present application when assessing whether the various aspects of the claimed subject-matter are new.

5. Comments with respect to item VIII

a) In view of the comments made at point 2.b) above, **claim 56** is objected to under Article 6 PCT.

b) In view of the last paragraph of page 29 which is deemed to correspond with claim 22, the claimed subject-matter appears not to be clearly defined. Therefore, **claim 22** is objected to under Article 6 PCT.

c) The term "system" as used in **claims 42 and 43** appears to be a term generally accepted in the field of the invention. Indeed, it is deemed that said claims aim at covering "kits". Therefore, also said claims are objected to under Article 6 PCT.

1. A composition produced by combining therapeutically effective amounts of:

(a) one or more complement-fixing human, recombinant human or humanized antibodies or fragments thereof that comprise a complement-binding Fc region of a complement-fixing antibody, which specifically bind to an epitope of a mammalian myelin selected from the group consisting of galactocerebroside (GalC), O4, Myelin Associated Glycoprotein (MAG), NOGO, NI220, NI-35/250, myelin oligodendrocyte glycoprotein (MOG) and arretin; and

(b) sufficient complement protein to initiate complement activation, wherein said complement protein comprises at least C3 and C4 and lacks one or more of the normal complement proteins;

wherein the combination is effective to cause focal transient disruption and/or transient demyelination of mammalian neurons.

2. A composition comprising:

(a) a first component comprising one or more complement-fixing human, human recombinant or humanized antibodies or fragments thereof that comprise a complement-binding Fc region of a complement-fixing antibody, which specifically bind to mammalian myelin epitope selected from the group consisting of a galactocerebroside (GalC), an O4, a myelin associated glycoprotein (MAG), a NOGO, a NI220, a NI-35/250, myelin oligodendrocyte glycoprotein (MOG) and an arretin; and

(b) a second component comprising sufficient complement protein to initiate complement activation, wherein said complement protein comprises at least C3 and C4 and lacks one or more of the normal complement proteins;

wherein combining the first component and the second component in situ or in vivo produces a formulation that is effective to cause focal transient disruption and/or transient demyelination of mammalian neurons.

3. The composition according to claim 1 or 2, wherein the second component comprises sufficient complement protein to allow complete activation of the complement cascade when the system is administered *in vivo* or *in situ*.

4. The composition according to any one of claims 1, 2 or 3, wherein said complement protein lacks one or more of C5, C6 and Factor B.

5. A two-part composition comprising:

(a) a first part comprising one or more complement-fixing human, human recombinant or humanized antibodies or fragments thereof that comprise a complement-binding Fc region of a complement-fixing antibody, which specifically bind to a mammalian myelin epitope selected from the group consisting of a galactocerebroside (GalC), an O4, a myelin associated glycoprotein (MAG), a NOGO, a NI220, a NI-35/250, myelin oligodendrocyte glycoprotein (MOG) and an arretin; and

(b) a second part sufficient complement protein to initiate complement activation, wherein said complement protein comprises at least C3 and C4 and lacks one or more of the normal complement proteins;

wherein the composition that results when the first part is combined with the second part *in situ* or *in vivo* is effective to cause focal transient disruption and/or transient demyelination of mammalian neurons.

6. The composition according to claim 5, wherein the second part comprises sufficient complement protein to allow complete activation of the complement cascade when the system is administered *in vivo* or *in situ*.

7. The composition according to claim 5 or 6, wherein said complement protein lacks one or more of C5, C6 and Factor B.

8. The pharmaceutical composition according to any one of claims 1, 2, 3 or 4, further comprising a physiologically acceptable carrier.

9. The composition according to any one of claims 1, 2, 3 or further comprising one or more growth factors.

10. The composition according to any one of claims 1, 2, 3 or 4, wherein one or more of the antibodies or fragments thereof comprise or are derived from a monoclonal antibody.

11. The composition according to any one of claims 1, 2, 3 or 4, wherein one or more of the antibodies or fragments thereof are labeled.

12. The composition according to any one of claims 1, 2, 3 or 4, wherein said fragments are selected from the group consisting of a Fab, a Fab', and a F(ab')2 domain of an antibody.

13. The composition according to any one of claims 1, 2, 3 or 4, wherein the antibodies or fragments thereof further comprise variable regions of an Fv domain linked by a disulfide bond or by a peptide linker.

14. The composition according to any one of claims 1, 2, 3 or 4, wherein the complement protein is heterologous to a species to which the composition is intended to be administered.

15. The composition according to any one of claims 1, 2, 3 or 4, wherein the complement protein is covalently or noncovalently attached directly or indirectly to said antibodies or fragments thereof, such that binding of said antibodies or fragments thereof to the surface of the mammalian myelin triggers an endogenous immune system attack.

16. The composition according to any one of claims 1, 2, 3 or 4, further comprising one or more growth factor or neurotrophic factor.

17. The composition according to claim 16, wherein the neurotrophic factor is FGF-1, GDNF, NGF, BDNF or NT3.

18. The composition as in claim 1, additionally comprising TNF

19. The composition according to any one of claims 1, 2, 3 or 4, wherein the antibodies or fragments thereof comprise or are derived from a polyclonal antibody.

20. The composition according to any one of claims 1, 2, 3 or 4, additionally comprising one or more inhibitors of one or more components of normal complement.

21. The composition according to any one of claims 1, 2, 3 or 4, additionally comprising:

(a) one or more chimeric proteins in which a first polypeptide which inhibits complement activation is linked to a second polypeptide which inhibits complement activation; or

(b) one or more polynucleotides encoding said one or more chimeric proteins.

22. The composition according to any one of claims 1, 2, 3 or 4, additionally comprising cells that secrete one or more nerve growth factors, neurotransmitters, neuropeptides, or enzymes involved in brain metabolism.

23. The composition as in claim 1, additionally comprising mononuclear phagocytes.

24. The composition according to any one of claims 1, 2, 3 or 4, additionally comprising cells for transplantation wherein said cells are selected from the list comprising: neural cells, paraneural cells, genetically modified non-neural cells, genetically modified non-neural cells that secrete neurally active molecules,

genetically modified foreskin fibroblast cells, cells selected from neural cell lines and cells derived from the adrenal medulla.

25. The composition according to claim 22 to 24, wherein said cells are allogenic, xenogenic or autologous.

26. The composition according to claim 24, wherein said neural cells are Schwann cells, astrocytes, oligodendrocytes, neurons or microglia.

27. The composition according to claim 24, wherein said paraneural cells are olfactory ensheathing glia.

28. The composition according to claim 24, wherein said cells are hybrid cells are prepared from somatic cell hybridization.

29. The composition according to any one of claims 22 – 28, wherein said cells are attached to a support matrix.

30. The composition according to claim 29, wherein said cells are co-cultured with glial cells and incubated with the support matrix prior to transplantation.

31. The composition according to claim 30, wherein the support matrix comprises material of synthetic or natural chemical substances or material of biological origin.

32. The composition according to claim 31, wherein the support matrix material is a silicon oxide, polystyrene, polypropylene, polyethylene, polyvinylidene fluoride, polyurethane, polyalginate, polysulphone, poly(tetrafluoroethylene-co-hexafluoropropylene), poly[N-(2-hydroxypropyl)methacrylamide], polyvinyl alcohol, acrylonitrile polymer, polyacrylamide, polycarbonate, polypentene,

nylon, amylase, gelatin, collagen, natural polysaccharide or modified polysaccharide.

33. The composition according to any one of claims 29 – 32, wherein the support matrix has an external surface that is coated with factors that promote cell adhesion, growth and/or survival.

34. The composition according to any one of claims 29 – 32, wherein the support matrix is constructed of porous material, wherein factors that promote cell adhesion, growth and/or survival are incorporated into the porous material.

35. The composition according claim 33 or 34, wherein said factors are cell adhesion molecules, fibronectin, laminin, collagen, elastin, glycosaminoglycans, proteoglycans or growth factors and/or bioactive fragments thereof.

36. The composition according to any one of claims 1, 2, 3 or 4, additionally comprising one or more CNS neural growth modulators or CNS neural growth modulator-secreting cells.

37. The composition according to any one of claims 1, 2, 3 or 4, additionally comprising one or more inhibitors of myelination, wherein said inhibitors are metalloproteases, inhibitors of apoptosis and/or necrosis, inhibitors of proinflammatory cytokines, activators of antiinflammatory cytokines, antiinflammatory cytokines, activators of antioxidants, generators of antioxidants or any combination thereof.

38. The composition according to any one of claims 1 – 37 designed for administration by a method chosen from the group comprising: injection, transplantation or perfusion

39. The composition according to any one of claims 1 – 37 designed for administration by a method that increases the level of phagocytosis.

40. A method for producing a composition, comprising the step of combining

(a) one or more complement-fixing human, recombinant human or humanized antibodies or fragments thereof that comprise a complement-binding Fc region of a complement-fixing antibody, which specifically bind to a mammalian myelin epitope selected from the group consisting of a galactocerebroside (GalC), an O4, a myelin associated glycoprotein (MAG), a NOGO, a NI220, a NI-35/250, myelin oligodendrocyte glycoprotein (MOG) and an arretin; and

sufficient complement protein to initiate complement activation, wherein said complement protein comprises at least C3 and C4 and lacks one or more of the normal complement proteins.

41. The method according to claim 38, wherein the complement protein is present in an amount sufficient to allow complete activation of the complement cascade when the composition is administered *in vivo* or *in situ*.

42. A system for promoting the transient demyelination of mammalian neurons comprising a composition in at least two separate containers, wherein a first container comprises one or more complement-fixing human, human recombinant or humanized antibodies or fragments thereof that comprise a complement-binding Fc region of a complement-fixing antibody, which specifically bind to a mammalian myelin epitope selected from the group consisting of galactocerebroside (GalC), O4, Myelin Associated Glycoprotein (MAG), NOGO, NI220, NI-35/250, Myelin Oligodendrocyte Glycoprotein (MOG) and arretin, and, a second container comprises sufficient complement protein to initiate complement activation, wherein said complement protein comprises at least C3 and C4 and lack one or more of the normal complement proteins.

43. The system according to claim 40, wherein the second container comprises sufficient complement protein to allow complete activation of the complement cascade when the system is administered *in vivo* or *in situ*.

44. Use of a composition according to any one of claims 1 – 39, to transiently disrupt and/or transiently demyelinate mammalian neurons and thereby promote neuron repair and/or growth in a mammal.

45. Use of the composition according to any one of claims 1 – 39, for the treatment of a neurological disorder in a mammal, wherein the composition is administered prior to, or concurrent with, cellular transplantation therapy.

46. Use of the composition according to any one of claims 1 – 39, to generate an environment within the CNS of a mammal that is permissive to growth of transplanted cells.

47. The use according to any one of claims 44 – 47, wherein said mammal has a neuron dysfunction.

48. The use according to claim 47, wherein the neuron dysfunction is caused by injury or trauma to the CNS.

49. The use according to claim 48, wherein the injury is a spinal cord injury.

50. The use according to claim 47, wherein the neuron dysfunction is caused by disease.

51. The use according to claim 50, wherein the disease is selected from the group consisting of Alzheimer's disease and Parkinson's disease.

52. The use according to claim 47, wherein the neuron dysfunction is chronic.

53. The use according to claim 44, wherein said neural growth regenerates structures lost due to injury, illness or those having incomplete or immature formation.

54. Use of the composition according to any one of claims 1 – 39 to facilitate grafting a cell in a mammal.

55. The use according to any one of claims 44 or 54, wherein the mammal is human.

56. Use of one or more complement-fixing antibodies or fragments thereof, which specifically bind to an epitope of myelin, and which are labeled, to detect and monitor the efficacy of the composition cause focal transient disruption and/or transient demyelination of mammalian neurons.

57. The composition according to any one of claims 1 – 39, contained within a biodegradable polymer microsphere.

58. The composition according to any one of claims 1 – 39, contained within an implant.

59. The composition according to any one of claims 1 – 39, contained within a pump.